

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:) Confirmation No.: 4282
)
Kenshi KAMEI et al) Art Unit: 1614
)
Appln. No.: 10/532,585) Examiner: P.G. Spivack
)
Filing Date: April 25, 2995) June 12, 2008
)
For: THERAPEUTIC AND/OR) ATTY.'S DOCKET: KAMEI=2
PREVENTIVE AGENT...)

**REPLY: THIRD REQUEST FOR RECONSIDERATION; SUBMISSION
OF DECLARATION AND OTHER EVIDENCE**

Customer Service Window, Mail Stop AMENDMENT
Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, 401 Dulany Street
Alexandria, Virginia 22314

Sir:

Applicants are in receipt of the Office Action
mailed December 12, 2007. Attached is a petition for three
(3) months' extension of time together with the petition fee.

Claims 10 and 15-19 remain in the application
without amendment. Attached hereto is a Declaration in lieu
of affidavit under 37 C.F.R 1.132 in the name of one of the
co-inventors, Dr. Kenichi Ozaki, as well as two one-page
documents, one entitled "The Migrating Motor Complex" and the
other entitled "Candidate GI Hormone: Motilin". Applicants
again respectfully request reconsideration of the present
application and allowance, based not only on the previous

Appln. No. 10/532,585

Reply: Third Request for Reconsideration;

Submission of Declaration and other

Evidence. dated June 12, 2008

Reply to Office Action of December 26, 2006

remarks of record, but also on the evidence submitted herewith and the additional remarks below.

Claims 10 and 19 have been rejected under Section 102 as anticipated by Koga et al, Drugs of The Future (Koga). This rejection, based on lack of novelty wherein obviousness is not an issue, is respectfully traversed.

The following statement appears in this rejection: "Koga teaches the administration of the compound of instant Formula I, which is designated GM-611, a motilin receptor agonist, to treat idiopathic constipation and constipation dominant irritable bowel syndrome", referring to the description on page 207, left column, lines 14 to 18 of the citation, which reads as follows:

"Some papers suggested the presence of motilin receptors on colonic smooth muscle, indicating potential therapeutic application of motilin agonists in idiopathic constipation and irritable bowel syndrome"

In this regard, it is clear that such description does not specifically refer to GM-611 at all. Further, the term "motilin agonists" in the context of Koga is understood to refer to Erythromycin A, since subsequent descriptions only refer to Erythromycin A (abbreviated to "EMA" therein). This

Reply: Third Request for Reconsideration;

Submission of Declaration and other

Evidence. dated June 12, 2008

Reply to Office Action of December 26, 2006

is confirmed in the first paragraph on page 2 of the attached Declaration of Dr. Ozaki. Therefore, the aforementioned statement in the rejection is clearly incorrect, since Koga includes no teachings relating to GM-611 used for treatment of idiopathic constipation or constipation dominant irritable bowel syndrome.

In addition, applicants have already submitted Bradette et al. (J. Gastrointest Mot. 1993, 5, 247-541), Jameson et al. (Aliment, Pharmacol. Ther. 1992, 6, 589-595) and Bassotti et al. (Z. Gastroenterol. 1998, 36, 209-213), which disclose the fact that erythromycin has no effect on colon motility.

Further, Koga also includes the following description:

"However, others reported that intravenously injected EMA failed to effectively stimulate colonic motility, except for the lowest dose investigated, in chronically constipated patients (36)."

In applicants' previous reply, applicants already referred to the above noted documents and stated "In light of the prior art disclosed in these documents, a person skilled in the art would naturally have considered the GM-611 would likely have no effect on the colonic motility as the parent

Reply: Third Request for Reconsideration;

Submission of Declaration and other

Evidence. dated June 12, 2008

Reply to Office Action of December 26, 2006

compound, erythromycin also has no effect, and therefore that GM-611 cannot reasonably be expected to succeed in the treatment of constipation, and thus cannot be applied to the treatment of constipation." (Further, the Examiner states in the present Office Action the Applicant' argument in response to the rejection set forth in the last Office is persuasive.)

In light of the foregoing, applicants believe and strongly maintain that the description on page 207, left column, lines 14 to 18 of Koga includes neither any description nor suggestion regarding application of GM-611 to constipation.

Regarding the Examiner's statement "The compound was shown to induce strong contractions in the stomach, and the contractions migrated caudally along the small intestine", applicants note that Koga includes the following description:

"GM-611 (01.-30 ug/kg, i.v.) induced strong contractions in the stomach in the fasting state, and the contractions migrated caudally along the small intestine."

(page 268, right column, lines 6 to 4 from the bottom)

The rejection seems to refer to such description, and thus incorrectly states, "Such an effect [contractions in the stomach in the fasting state, migrating along the small intestine] would have resulted in an acceleration of

defecation." However, Koga also states, "This pattern of contractions was similar to that of motilin" (page 268, right column, lines 4 to 3 from the bottom). Namely, the contractions are similar to "migrating motor complex (MMC)", which is caused by motilin in the fasting state. Actually, such contractions do not occur in the digestive state (Koga, page 269, left column, lines 12 to 30). This is confirmed in the third paragraph of page 2 of Dr. Ozaki's attached declaration. Further, Koga discloses that GM-611 caused strong contractions in humans and dogs, similarly to MMC (page 269, right column, lines 30 to 35).

MMC is initiated in the stomach triggered by an increase of the plasma motilin level in the fasting stage, and strong contractions migrate to terminal ileum (please note the attached document titled "Candidate GI Hormone: Motilin").

GM-611 is expected to induce strong contraction like MMC, since it is known as a motilin agonist. However, there is no disclosure in Koga or anywhere else (or any teaching or suggestion) that such contractions affect the colon in any way. Indeed, Koga states that "in the fasting state, bursts of strong contractions (MMC or Migrating Motor Complex) occur periodically in the stomach and migrate to the lower small intestine (page 268, lines 26 to 29), but includes no

Reply: Third Request for Reconsideration;

Submission of Declaration and other

Evidence. dated June 12, 2008

Reply to Office Action of December 26, 2006

reference to influences or extensions thereof to the colon.

No known prior art discloses or suggests that MMC accelerates defecation (see the last three paragraphs on page 2 of Dr. Ozaki's attached declaration).

In addition, there is no teaching or suggestion regarding relationship between the MMC and an acceleration of defecation or treatment for constipation. Please be advised that MMC is also known as the cause of growling in the stomach (please note to the attached document titled "The Migrating Motor Complex"). Applicants believe that the Examiner should agree that such gastrointestinal contractions, which only occur in the fasting stage and may cause noises from the stomach, have no relation to acceleration of defecation or treatment for constipation. Applicants also believe that this would be known to a person skilled in the art at the time of the priority date.

Therefore, applicants believe and again strongly respectfully submit that the description in Koga regarding strong contractions like MMC induced by GM-611 does not provide a skilled person with any disclosure, teaching, motivation or suggestion for the claimed subject invention.

Claims 10 and 19 call for a method for treating constipation. Koga simply does not disclose any such method.

Claims 10 and 19 define novel subject matter, and the rejection should be withdrawn. Such is respectively requested.

Claims 10 and 15-19 have been rejected under Section 103 as being obvious from Koga.¹ This rejection is respectively traversed.

As pointed out above, and contrary to what is stated in the rejection, Koga does **not** teach that a compound of Formula I, GM-611, is administered to treat idiopathic constipation and constipation dominant irritable bowel syndrome. Accordingly, the rejection is based on faulty premises.

The rejection is also incorrect in the statement that contractions which migrate caudally along the small intestine would have been expected to result "in an acceleration of defecation" as stated in the last sentence on the second paragraph on page 3 of the Office Action. Defecation of course proceeds from the **large** intestine (the colon), not the small intestine. Please consider the bottom

¹ In so far as concerns claims 10 and 19, this rejection is inconsistent with the rejection based on Section 102. A reference can either anticipate or make a claim obvious, but a reference cannot do both bearing in mind the clear language of 35 U.S.C. 103 which states that a "patent may not be obtained though the invention is not identically disclosed or described as set forth in Section 102 of this title,"

three paragraphs on page 2 of Dr. Ozaki's attached Declaration executed May 22, 2008.

In the third paragraph on page 3 of the Office Action, the rejection states: "In all cases, the presence of motilin receptors on colonic smooth muscle provides a potential therapeutic application GM-611." Respectfully, this statement is speculation based on applicants' own disclosure and not based on any prior art.

Regarding the above statement in the present rejection, applicants cannot find any description in Koga supporting the statement regarding "the presence of motilin receptors on colonic smooth muscle." Accordingly, there is no basis for such statement.

As already pointed out in previous remarks, there are documents reporting the difference of motilin receptor expressions between species. In particular, Jameson et al. (Aliment Pharmacol. Ther. 1992, 6, 589-595) describes the motilin receptors may be absent in the human colon. (Further, again, the Examiner admits in the present Office Action that the previous argument is persuasive.)

In light of the foregoing, applicants believe and respectfully submit that the statements as noted above in the present Office Action are groundless. Applicants strongly

Appln. No. 10/532,585
Reply: Third Request for Reconsideration;
Submission of Declaration and other
Evidence, dated June 12, 2008
Reply to Office Action of December 26, 2006

submit that Koga does not disclose any teaching or suggestion regarding the subject invention, and that a person skilled in the art could not have conceived the subject invention, by referring to Koga.

Withdrawal of the rejection is in order and is respectfully requested.

Favorable reconsideration and allowance are respectfully urged.

Respectfully submitted,

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